Benzyltrimethylammonium chloride

CAS # 56-93-9

Test plan justification

Bayer Chemicals LLC

November 14, 2003

Executive Summary

Bayer Chemicals LLC (Bayer) hereby submits for review and public comment their test plan for Benzyltrimethylammonium chloride (CAS# 56-93-9) under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program.

IUPAC Name	Abbreviation	CAS#
N,N,N-trimethyl-benzenemethanaminium chloride	BTMAC	56-93-9

BTMAC is used as:

A solvent for cellulose; a gelling inhibitor in polyester resins; an intermediate (Lewis, RJ 1997); a dye assistant for acrylics (Syracuse Research Institute); and a Phase-transfer agent (Ashford, R.D. 1994).

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, Bayer has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. Existing data indicates that this chemical is of low concern for aquatic toxicity, low concern as Persistent Organic Pollutants, and of high concern for mammalian toxicity. Bayer concludes that there is sufficient, reliable data on BTMAC except for Developmental toxicity. **An OECD 414 study is recommended for fulfilling the endpoints of the HPV Program.**

Data Review

Physicochemical properties:

The properties of BTMAC can be found in Handbooks such as Hawley's Condensed Chemical Dictionary. BTMAC is a liquid at ambient temperatures, with a freezing point of -50ºC and boiling point and decomposition temperature of 135ºC. The measured octanol/water partition coefficient is -2.17 and it is highly soluble in water. A calculation for vapor pressure resulted in 0.0000000308 hPa (0.0000000231mm Hg) at 25ºC. Data is available for all endpoints, no additional testing is proposed for purposes of the HPV Program (See Table 1 and IUCLID document).

Environmental Fate:

BTMAC was calculated to have a photodegradation half-life of 7.4 hours. Fugacity modeling demonstrates partitioning to the soil and water compartments, negligible amounts to air and sediment. A biodegradation study demonstrated that BTMAC and other quaternary ammonium compounds are not readily biodegradable and at high concentrations may be toxic to the microbial sludge. However, acclimation profoundly influences the biodegradability and therefore these compounds should not be considered persistent. BTMAC is very stable in water, confirmed by the marketed product being an aqueous solution. No additional testing is proposed for purposes of the HPV Program (See Table 1 and IUCLID document).

Ecotoxicology:

Aquatic studies have been performed on the aquatic invertebrate, *Daphnia pulex* and two species of algae. *Daphnia* appear to be the most sensitive species: LC_{50}= 11.94 mg/l as compared to 14 day EC_0 of *Anabaena variabilis* and *Oscillatoria* species of 1857 mg/l. There are no studies on fish, however ECOSAR estimates that fish are less sensitive than *Daphnia* or algae. Therefore an additional animal study would not provide additional information that would be useful or relevant. No additional testing is proposed for purposes of the HPV Program (See Table 1 and IUCLID document).

Mammalian Toxicology:

Acute toxicity studies show that BTMAC is toxic by the oral route of exposure in rats (LD_{50} = 180 mg/kg). Acute toxicity of BTMAC was characterized by severe cholinergic symptoms including salivation, chromodacryorrhea, and sedation. (See Table 1 and IUCLID document).

There are multiple studies to fill the Mutagenicity endpoints, both *in vitro* and *in vivo*. Ames results were consistently negative; a chromosome aberration study using Chinese hamster lung cells was ambiguous; and an *in vivo* mouse micronucleus test

revealed a positive increase in micronuclei that was significantly different from the control only the highest dose tested (100 mg/kg). (See Table 1 and IUCLID document).

There are several repeated dose toxicity studies (28 day and 90 day) by the oral route of exposure in rats and mice. A NOAEL of 25 mg/kg/day was determined. Some cholinergic effects including chromodacryorrhea, lacrimation, salivation, pupillary constriction, altered gait, and mild tremors were observed at non-lethal doses (See Table 1 and attached IUCLID document).

At the end of the 90 day study, in both rats and mice, samples were collected for sperm motility and vaginal cytology evaluations. No treatment-related differences were detected in reproductive tissue evaluations or estrous cycle characterizations, except in female rats where a minimal shortening of diestrus and prolongation of proestrus occurred in the 25 mg/kg females with no alteration in the length of the estrous cycle. There was no Developmental study located, therefore an OECD 414 is proposed. (See Table 1 and attached IUCLID document).

There is data to cover all SIDS endpoints, except for Developmental toxicity. An OECD 414 study is recommended for fulfilling the endpoints of the HPV Program (See Table 2).

Conclusion

Existing data indicates that this chemical is of low concern for aquatic toxicity, low concern as Persistent Organic Pollutants, and high concern for mammalian toxicity. Bayer concludes that there is sufficient, reliable data on BTMAC except for Developmental toxicity. An OECD 414 study is recommended for fulfilling the endpoints of the HPV Program.

Table 1. Available data for BTMAC (CAS# 56-93-9)

Endpoint	Result	Method/Reference*
Physical-Chemical Data		
Melting Point	-50º C	Handbook value
Boiling Point	> 135º C	Handbook value
Vapour Pressure	0.0000000308 hPa	MPBPWin v1.41
Partition Coefficient ($logP_{ow}$)	-2.17	Hansch & Leo, 1995
Water Solubility	Highly soluble	Handbook value
Environmental Fate		
Photodegradation	½ life = 7.4 hours	AOPWin calculation
Fugacity	Air = < 0.1% Water = 45.3% Soil = 54.6% Sediment = < 0.1%	EPIWin Fugacity Level III calculation
Biodegradability	0% after 10 days	Urano & Katz, 1986
Water Stability	stable	Sold as an aqueous solution
Ecotoxicology		
Acute Fish Toxicity (96 hrs)	No data	
Acute Invertebrate Toxicity (48 hrs)	LC50 = 11.94 mg/l	EPA OPP 72-2
Algal Toxicity (14 days)	LC0 = 1875 mg/l	Rucka, et al., 1980
Mammalian Toxicology		
Acute Toxicity	180 mg/kg bw (oral, rat)	Sanders, et al., 1995
Mutagenicity	negative	Ames
Chromosome Aberration	Ambiguous positive	Chinese Hamster lung cells Mouse micronucleus test
Repeated Dose Toxicity	NOAEL = 25 mg/kg/day (Rat and mouse, oral, 90 days)	EPA OPP 82-1
Reproductive Toxicity	No adverse effects on reproductive organs (Rat and mouse, oral, 90 days)	EPA OPP 82-1
Developmental Toxicity	No data	

* Robust summaries and References can be found in the IUCLID document.

Table 2. Test Plan for BTMAC (CAS# 56-93-9)

Endpoint	Data Availability	Acceptable	Planned testing
Physical-Chemical Data			
Melting Point	✓	✓	
Boiling Point	✓	✓	
Vapour Pressure			
Partition Coefficient ($logP_{ow}$)	✓	✓	
Water Solubility	✓	✓	
Environmental Fate			
Photodegradation	✓	✓	
Fugacity	✓	✓	
Biodegradability	✓	✓	
Water Stability	✓	✓	
Ecotoxicology			
Acute Fish Toxicity			Derogation statement: less sensitive species
Acute Invertebrate Toxicity	✓	✓	
Algal Toxicity	✓	✓	
Mammalian Toxicology			
Acute Toxicity	✓	✓	
Mutagenicity	✓	✓	
Chromosome Aberration	✓	✓	
Repeated Dose Toxicity	✓	✓	
Reproductive Toxicity	✓	✓	
Developmental Toxicity			OECD 414

✓ = data available and considered adequate.

References

Ashford, R.D. 1994. Ashford's Dictionary of Industrial Chemicals. London, England: Wavelength Publications Ltd., 1994. 124

Hansch C, Leo A, and Hoekman D. 1995. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society. p.79.

Lewis, RJ Sr (Ed.). 1997. Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. 133.

Rucka M, Oswiecimska M, et al. 1980. New Biocides for Cooling Water Treatment. Environ. Protection Engin. 6(4):455-464.

Sanders JM, Griffin RJ, Burka LT, and Matthews HB. 1995. Toxicokinetics of the cholinomimetic compound benzyltrimethylammonium chloride in the male rat and mouse. Xenobiotica. 25(3):303-313.

Urano, K and Katz Z. 1986. Evaluation of Biodegradation Ranks of Priority Organic Compounds. J. Haz. Mat. 13:147-159.

Additional References can be found in the IUCLID document.